

Letter to the Editor

Enhancing naloxone provision in patients with comorbid mental illness and opioid use disorder amidst the rise of nitazenes in Ireland

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Sir,

Existing research shows that approximately 50% of patients with severe mental illness have a comorbid substance use disorder (Drake *et al.* 2007). Among the most vulnerable of these patients are those with comorbid opioid use disorders. The HSE National Drug Treatment Centre (NDTC) in Dublin city centre is responsible for the care of many of these vulnerable “dual diagnosis” patients and as such finds itself at the forefront of a new challenge – the rise of synthetic opioids.

In Ireland, drug-related deaths increased year on year from 2016 to 2020 (Hanrahan *et al.* 2022). In 2021 there were 354 deaths, with seven out of ten involving opioids and eight in ten involving more than one substance (Kelleher *et al.* 2024). Since late 2023, the Irish illicit drug market has seen the emergence of *nitazenes*, new and highly potent synthetic opioids, with a number of associated overdose clusters (Killeen *et al.* 2024). Naloxone, an opioid antagonist, is known to have been administered in multiple locations by first responders and is thought to have saved lives.

The “opioid crisis” that has swept across the USA and Canada in recent years has been largely attributed to the synthetic opioid fentanyl. In the USA in 2022 alone, there were more than 109000 deaths due to drug overdoses, with over 70% of these attributable to illegally manufactured fentanyl and fentanyl analogues (Tanz *et al.* 2024). While fentanyl is far less prevalent on this side of the Atlantic, demand and supply issues render Europe vulnerable to the emergence of a synthetic opioid market.

Post-COVID-19 pandemic inflation and the associated cost-of-living crisis have resulted in increasing numbers of people contending with poverty, homelessness and addiction. Afghanistan, historically the source of up to 90% of Europe’s heroin supply, has exited the global supply chain. In 2022, the cultivation of the opium poppy was outlawed by the Taliban, with hundreds of thousands of hectares of poppy fields destroyed (Mansfield, 2023). As existing heroin stockpiles are consumed, there will likely be significant implications for the European illicit opioid market, with criminal gangs looking towards alternative suppliers (Giraudon *et al.* 2024).

The scheduling of new illicit substances naturally lags behind their production, and chemists will continue to develop new compounds to circumvent existing laws. Nitazenes are synthetic opioids which were initially developed in the 1950s (Gross and

Turrian, 1957), but were never approved for therapeutic purposes, largely due to their extremely high potency and the high risk of producing dependency. Relative to heroin, the potency of the various nitazene analogues varies from 50 to 500 times stronger (Holland *et al.* 2024; Ujváry 2021), with users at a considerably higher risk of overdose.

Nitazenes were first identified in Europe in 2019 (Krotulski *et al.* 2020) and on the island of Ireland in 2022. In 2023, nitazenes were implicated in six deaths in Northern Ireland (McCauley, 2023). In November and December 2023, there were two significant clusters of non-fatal opioid overdoses in the Irish cities of Dublin and Cork (Killeen *et al.* 2024). In total at least 77 people were known to have been affected, with *N-pyrrolidino protonitazene* implicated in a number of these overdoses. In 2024, nitazenes were implicated in at least three subsequent overdose clusters in the Republic of Ireland. Nitazenes have been detected in various forms, including powders cut with heroin, cocaine, and ketamine; street benzodiazepines; counterfeit oxycodone tablets; cannabis products; and blotting paper (Public Health Scotland, 2024; WEDINOS, 2023).

The opioid antagonist naloxone has been found to be highly effective in reversing the physiological effects of nitazene-related overdoses and thus the associated respiratory depression. The amount of naloxone needed to reverse an overdose may be higher when nitazenes are implicated (Amaducci *et al.* 2023). Naloxone is available through many additions services nationwide; however, uptake is often low. A recent audit and intervention carried out at the HSE NDTC resulted in a significant improvement in the uptake of take-home naloxone kits from 12% to 61% in a cohort of service users. Appointments were made for all patients with a doctor or pharmacist, in which one-to-one training in emergency overdose management and administration of naloxone was delivered. Naloxone kits were then prescribed and dispensed to willing patients who successfully completed the training.

Integrating naloxone provision into routine care for patients receiving opioid agonist treatment (OAT) is of crucial importance, along with the implementation of targeted interventions to address barriers to naloxone uptake. Such strategies may include expanding access to naloxone through peer-to-peer training, addressing misconceptions and stigma surrounding naloxone use and distribution of naloxone through patients’ social networks.

In patients with a dual diagnosis, the interplay between severe mental illness and substance misuse heightens risk of drug interaction and overdose, complicates treatment adherence, and exacerbates psychopathology (De Carvalho and Garner, 2019). Additionally, patients with symptoms of active mental illness are

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less likely to engage with harm reduction programmes due to paranoia, disorganised behaviour and negative symptoms. It is therefore important that OAT providers work in collaboration with statutory, NGO and community-based harm reduction initiatives with a focus on assertive outreach.

On a national level, consideration could be given by government to pass legislation making naloxone available over the counter in pharmacies, a strategy that has seen success in a number of European countries (EMCDDA, 2023). In August 2023, the Irish Prison Service in conjunction with the HSE introduced a new initiative in which vulnerable prisoners received a takeaway intranasal naloxone kit on their release, historically an extremely vulnerable time for overdose (Irish Prison Service, 2023).

Dual diagnosis patients are extremely vulnerable to the devastating effects of synthetic opioids like nitazenes. Preparedness is key. By enhancing access to naloxone, integrating mental health and addiction services, and addressing systemic barriers, we can mitigate overdose risks and improve outcomes for this high-risk population. The increase in take-home naloxone for this vulnerable population following the targeted intervention in the NDTC is reassuring in this regard and services should prioritise this intervention with dual diagnosis patients.

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